

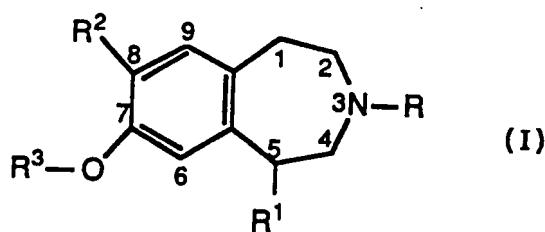


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<p>(21) International Application Number: PCT/US91/04046</p> <p>(22) International Filing Date: 13 June 1991 (13.06.91)</p> <p>(30) Priority data: 538,965 15 June 1990 (15.06.90) US</p> <p>(60) Parent Application or Grant (63) Related by Continuation US 538,965 (CIP) Filed on 15 June 1990 (15.06.90)</p> <p>(71) Applicant (for all designated States except US): SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).</p> <p>(72) Inventors; and (75) Inventors/Applicants (for US only) : CHANG, Wei, Kong [US/US]; 63 West Cedar Street, Livingston, NJ 07039 (US). KOZLOWSKI, Joseph, A. [US/US]; 36 Maple Avenue, Plainsboro, NJ 08536 (US). LOWE, Derek, B. [US/US]; 101B Tierney Drive, Cedar Grove, NJ 07009 (US). BERGER, Joel, Gilbert [US/US]; 50 West Lindsay Road, Cedar Grove, NJ 07009 (US).</p>		<p>(74) Agents: HOFFMAN, Thomas, D et al.; Schering-Plough Corporation, One Giralta Farms, Madison, NJ 07940-1000 (US).</p> <p>(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC, MG, ML (OAPI patent), MR (OAPI patent), MW, NL (European patent), NO, PL, RO, SD, SE (European patent), SN (OAPI patent), SU, TD (OAPI patent), TG (OAPI patent), US.</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>	

(54) Title: 8-LOWER ALKYL-5-CYCLOALKYL OR 5-CYCLOALKENYL SUBSTITUTED BENZAZEPINES AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abstract

Disclosed herein are novel 8-loweralkyl-5-cycloalkyl or 5-cycloalkenyl 2,3,4,5-tetrahydro-1*H*-3-benzazepines of general formula (I), wherein R, R¹, R², and R³, are specified substituents. R and R² are preferably CH₃, R³ is preferably H and R¹ is preferably cyclohexenyl. The compounds of the formula (I) as well as pharmaceutical compositions comprising them are indicated as being useful orally in the treatment of psychoses, depression and pain.

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8-LOWER ALKYL-5-CYCLOALKYL OR
5-CYCLOALKENYL SUBSTITUTED BENZAZEPINES AND
PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

BACKGROUND OF THE INVENTION

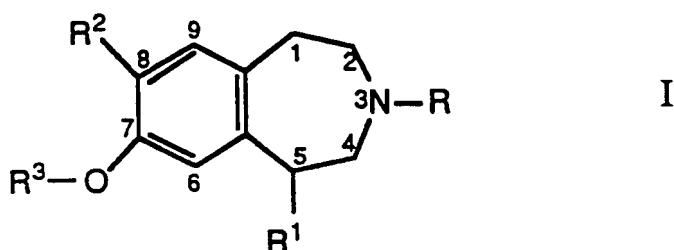
- This invention relates to novel 8-lower alkyl-5-cycloalkyl or 20 5-cycloalkenyl substituted-2,3,4,5-tetrahydro-1H-3-benzazepines, and to pharmaceutical compositions containing them. The compounds are orally active and have valuable pharmaceutical properties in the treatment of psychoses, depression, pain and hypertension.
- Substituted 5-phenyl-2,3,4,5-tetrahydro-1H-3-
- 25 benzazepines have been described in the art. For example, see U.S. Patents 3,393,192, 3,609,138, 4,011,319, 4,284,555 and 4,477,378 as well as British Patent 1,118,688. The activities discussed for the compounds disclosed in these patents include antibacterial effects, central nervous system effects and hypotensive effects.
- 30 Weinstock et al. in Drugs of the Future, Vol. 10, No. 8, pp 645697 (1985) discuss the profound effect that 5-phenyl substituents have on the dopaminergic activity of certain types of benzazepines. See Table II on page 686.
- European Patent Application No. 83105610.6 (Publication 35 No. 0 096 838) discloses certain 5-aryloxy substituted 2,3,4,5-tetrahydro-3-benzazepines having H and/or alkoxy substituents in the 7- and 8- positions thereof. These compounds are disclosed as having utility in the treatment of depression.
- U.S. Patent Application Serial No. 07/322,801, filed 13 40 March 1989, discloses 5-substituted-2, 3, 4, 5-tetrahydro-1H-3-benzazepines lacking such a 5-phenyl substituent provide good anti-dopaminergic activity, and in particular, show surprising selectivity for the D-1 subclassification of dopaminergic receptors. The compounds of

this invention are generically, but not specifically disclosed in this U.S. patent application.

5

SUMMARY OF THE INVENTION

It has now surprisingly been found that certain novel 8-lower alkyl-5-cycloalkyl or 5-cycloalkenyl benzazepines have superior duration of action via oral administration for treating psychoses in mammals. Accordingly, in one of its aspects, the present invention 10 provides novel benzazepines of the structural formula I:



and the pharmaceutically acceptable salts thereof, wherein:

15

R represents H, (C₁-C₄)alkyl, allyl or cyclopropylmethyl;

R¹ represents (C₃-C₄, C₅-C₇ or C₈)cycloalkyl or (C₅-C₈)cycloalkenyl;

R² represents (C₁-C₄)alkyl;

20

R³ represents R², H, R²CO or ArNHCO;

Ar represents unsubstituted phenyl or phenyl substituted by one or more of, preferably one, two or three of, halogen, R², CF₃, NH₂, NHR², NR²R² or NO₂; or combination thereof.

25

The compounds of formula I possess analgesic, anticholinergic, antiaggressive and general tranquilizing properties. The invention therefore includes pharmaceutical compositions comprising a compound of formula I in combination with a pharmaceutically acceptable carrier and methods for treating mental disorders including psychoses, schizophrenia or depression in a mammal, or for the control of pain or anxiety in a mammal by administering, especially by the oral route, an effective amount of a compound of formula I to the affected mammals.

The invention also provides the use of a compound of formula I for the preparation of a pharmaceutical composition for use in

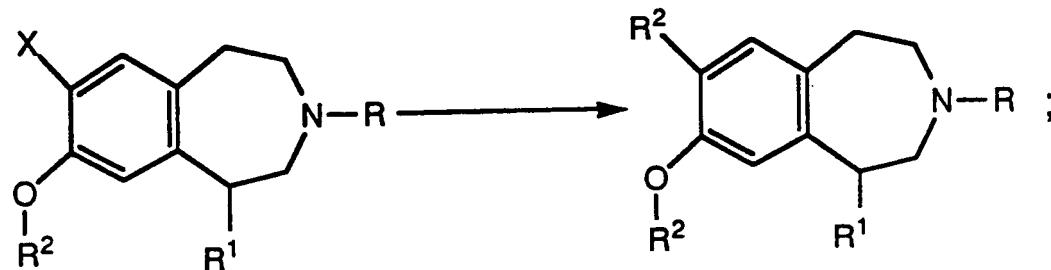
treatment of psychoses or depression, or for effecting analgesia, in particular, for use as an antipsychotic.

5 The invention also provides a method of treatment selected from one of the following method (a) to (c):

- 10 (a) treating psychoses in a mammal by administering to the mammal an antipsychotic effective amount of a compound of formula I, or a pharmaceutical composition thereof
- 15 (b) treating depression in a mammal by administering to the mammal an antidepressive effective amount of a compound of formula I or a pharmaceutical composition thereof, and
- 20 (c) providing for analgesia in a mammal by administering to the mammal an analgesically effective amount of a compound of formula I or a pharmaceutical composition thereof.

25 The present invention also provides a process for the preparation of a compound represented by formula I of claim 1 which process comprises a process selected from the following process A to C:

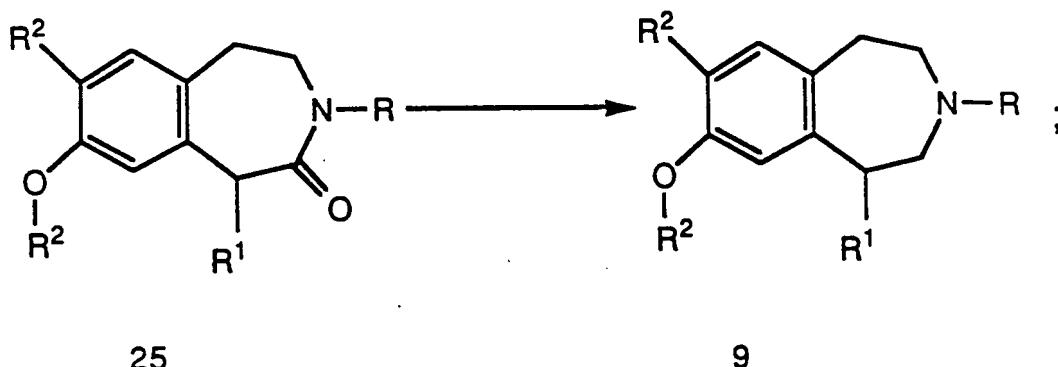
A: alkylation of a compound of formula 8 to form a compound of formula 9



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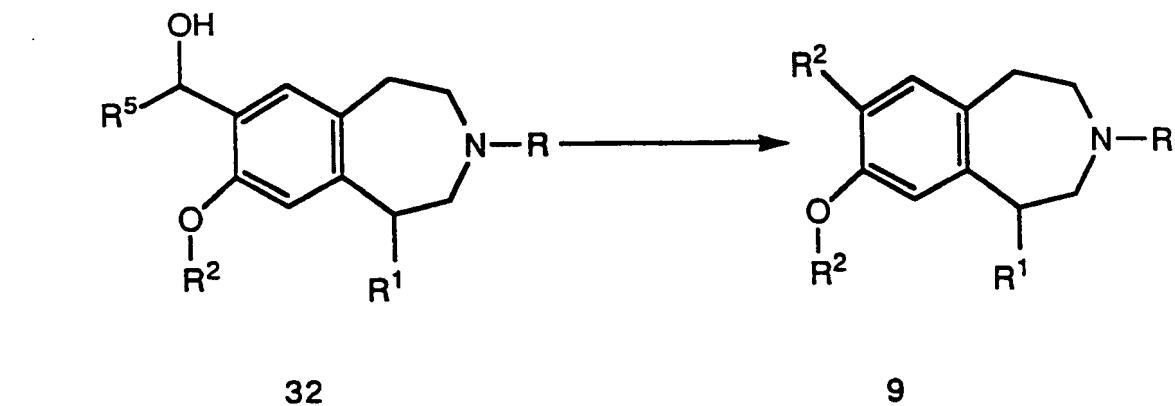
30 B: Reduction of a compound of formula 25 to form a compound of formula 9,



5

and

C: Reduction of a compound of formula 32 to form a compound of formula 9,



10

wherein R¹, R², R³ and R are as defined in claim 1, R⁵ is (C₁-C₃) alkyl or H and said process is followed as desired by conversion of compound 9 into compound of formula 1.

15

DETAILED DESCRIPTION OF THE INVENTION

When utilized herein and in the appended claims, the following terms, unless otherwise specified, have the following scope:

20

halo - represents fluoro, chloro, bromo or iodo;

alkyl - represents straight or branched carbon chains

having 1 to 4 carbon atoms:

cycloalkyl - represents a saturated carbocyclic ring

containing from 3, 4, 5, 7 or 8 carbon atoms:

25

cycloalkenyl - represents a carbocyclic ring containing at least one carbon-carbon double bond and having 5 to 8 carbon atoms. Typical suitable cycloalkenyl groups include 1-, 2-, and 3-

- 5 cyclopentenyl, 1-, 2-, 3-cyclohexenyl, 1,2-,1,3- 2,4- and 1,4-
 cyclohexadienyl, 1-, 2-, 3-, 4- cycloheptenyl, 1,3-, 1,4-, 2,6-, 2,4-;
 and 2,5- cycloheptadienyl, 2,4,6-and 1,3,5-cycloheptatrienyl, 1-,
 2-, 3-, 4-cyclooctenyl, 1,3-, 1,4-, 1,5-, 2,5-, 2,4-, 3,5-, 2,6 and inter
 alia cyclooctatrienyl such as 1,3,5- and 1,3,7-cyclooctatrienyl and
 1,3,5,7-cyclooctatetraenyl;
- 10 substituted phenyl - represents phenyl mono- or di-or tri-
 substituted by (C₁-C₄) alkyl, halo especially fluoro or chloro, CF₃,
 NH₂, NR²H, NR²R² or NO₂ or combinations thereof;
- 15 In one preferred embodiment of the invention, R represents
(C₁-C₄)alkyl, R¹ represents (C₅-C₈) cycloalkenyl or cycloalkadienyl,
R² represents (C₁-C₄) alkyl and R³ represents H.
- 20 In a further preferred embodiment of the invention, R and
R² each represent CH₃, R¹ represents cyclohexenyl preferably
cyclohex-2'-en-1'-yl or cyclohexadienyl and R³ represents H.
- 25 Preferred compounds of the general formula I include:
 (\pm)-5-cyclopent-3'-en-1'yl-3,8-dimethyl-2,3,4,5- tetrahydro-
1H-3-benzazepine-7-ol,
 (\pm)-5-(cyclohex-1'-en-1'yl)-3,8-dimethyl-2,3,4,5-tetrahydro-
1H-3-benzazepine-7-ol,
 (\pm)-5-(cyclohex-2'-en-1'-yl)-3,8-dimethyl-
2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,
 (\pm)-5-cyclopentyl-3,8-dimethyl-2,3,4,5- tetrahydro-1H-3-
benzazepin-7-ol,
 (\pm)-5-(cyclopent-1'-en-1'yl)-3,8-dimethyl- 2,3,4,5-
tetrahydro-1H-3-benzazepin-7-ol,
 (\pm)-5-(cyclopent-2'-en-1'yl)-3,8-dimethyl- 2,3,4,5-
tetrahydro-1H-3-benzazepine-7-ol,
 (\pm)-5-(cyclopent-3'-en-1'yl)-3,8-dimethyl- 2,3,4,5-
tetrahydro-1H-3-benzazepine-7-ol,
 (\pm)-5-(cyclohepta-2',4',6'-trien-1'yl)-3,8- dimethyl-2,3,4,5-
35 tetrahydro-1H-3-benzazepin-7-ol, and the stereoisomers thereof;
 and the pharmaceutically acceptable salts thereof.

Many compounds of the invention have at least one chiral center at C-5 and thus may exist in isomeric forms. The invention

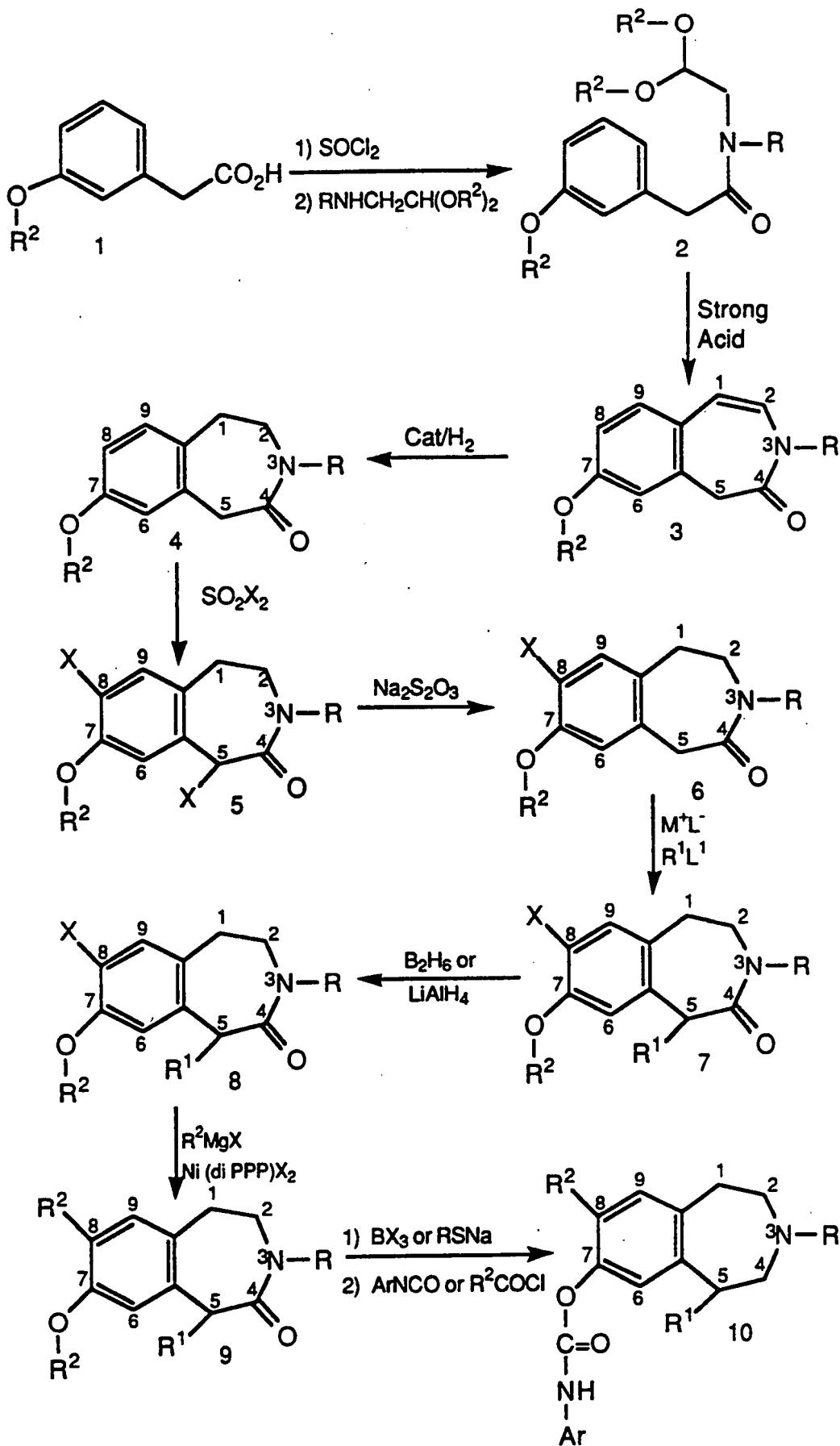
contemplates all such isomers both in pure form and in admixture, including racemic mixtures and mixtures of diastereoisomers.

5 Compounds of formula I can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemihydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of this invention.

10 The compounds of formula I may form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the salts are otherwise equivalent to their respective free base forms for purposes of the invention.

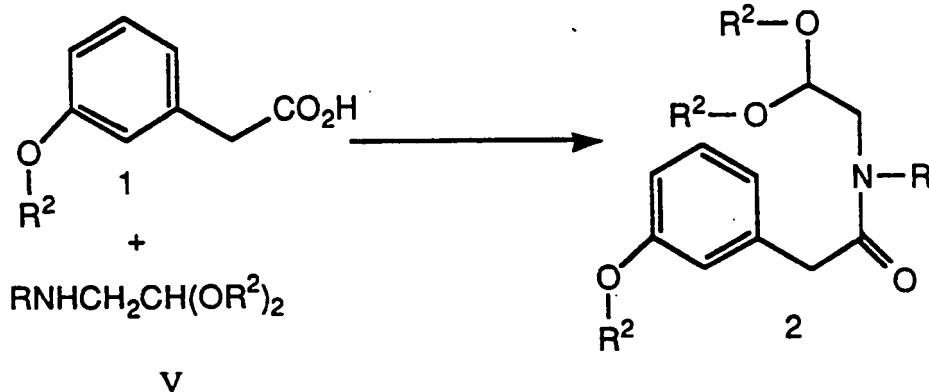
15 20

25 The compounds of formula I above may be prepared of the methods of Schemes A, B and C described below:

SCHEME A

The compounds of formula I may be prepared by the sequence of steps illustrated in Scheme A.

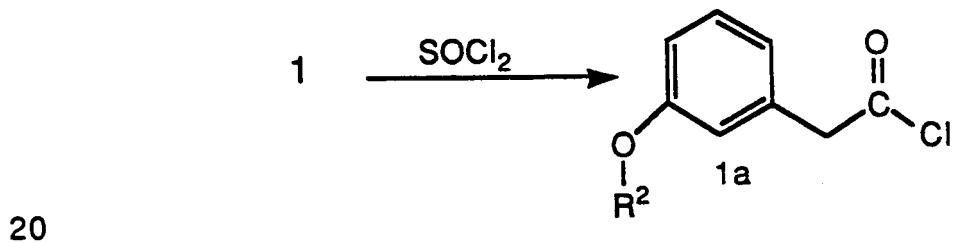
For example, a compound of formula 1 below may be
5 reacted with a compound of formula V to form a compound of formula 2:



wherein R² is an alkyl group, such methyl or ethyl.

10 This reaction may be performed at any suitable temperature, e.g., from about 0°C to about 50°C. Usually an inert solvent such as DMF, CH₂Cl₂, etc., is employed but the reaction may also be run neat. The reaction is run in the presence of coupling agents or dehydration agents such as dicyclohexylcarbodiimide, N-ethyl-N'-
15 (dimethylamino)ethylcarbodiimide, etc.

Alternatively, the compounds of formula 2 can be made by reacting the compounds of formula 1 with, for example, SOCl₂ or (COCl)₂ to yield the acid chloride of formula 1a

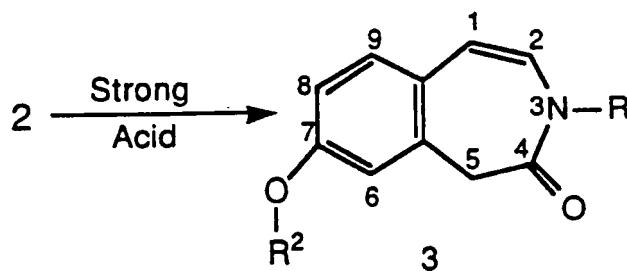


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which is then reacted with a compound of formula V. In this reaction, there is no need for a coupling agent.

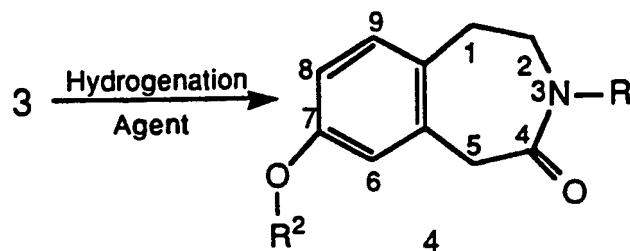
Compounds of formula 1 are either known or may be
25 prepared by techniques conventional in the art. The acetals of formula V are likewise known or easily prepared by conventional techniques in the art. See for example U.S. patent No. 4,490,369.

The acetal of formula 2 is reacted with a strong acid such as CF₃SO₃H, or HCl, to produce a compound of formula 3:

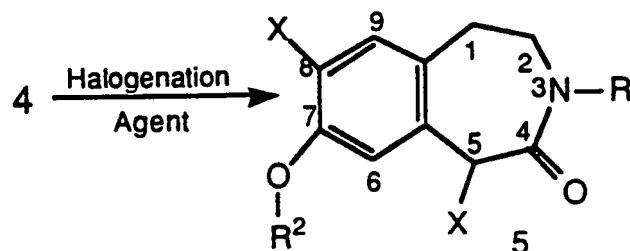


5 This reaction may be run neat, i.e., with the acid as the solvent, or in the presence of a solvent such as acetic acid. Any suitable temperature may be employed, e.g., from about 0°C to about 50°C.

10 The compounds of formula 3 are then reduced to a compound of formula 4 by employing a suitable hydrogenation agent which will reduce the olefinic bond of formula 3 without reducing the carbonyl thereof, e.g., H₂/PtO₂, H₂/Pd-C, etc.:

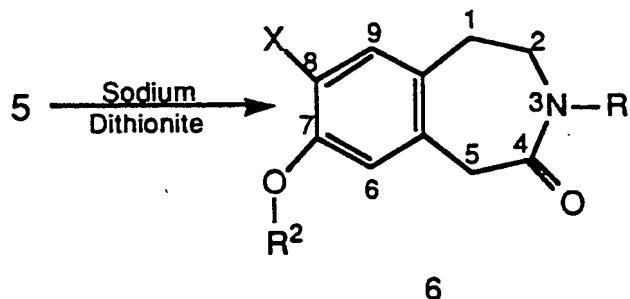


15 The compound of formula 4 is reacted with a halogenation agent such as SO₂X₂, e.g., SO₂Cl₂, or SO₂Br₂, to produce a compound of formula 5:



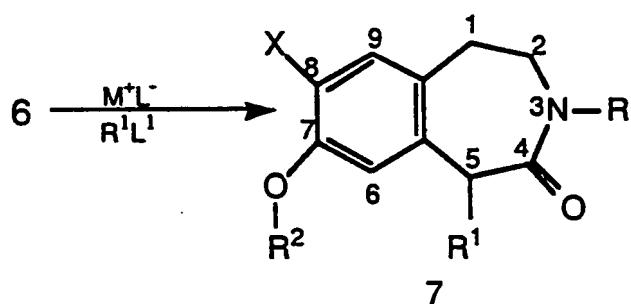
20 This reaction may be run at any suitable temperature and is usually performed in an inert solvent such as CH₂Cl₂, or CHCl₃.

25 The compound of formula 5 is reacted with a reducing agent, e.g. sodium dithionite in inert solvent, e.g. aqueous DMF at room temperature to remove the 5-halo group to form a compound of formula 6:



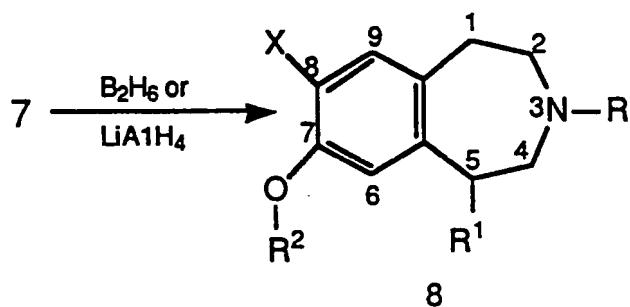
5 The compound of formula 6 may be reacted in an electrophilic substitution reaction with a compound of the formula R^1L^1 wherein L^1 is a leaving group such as a halogen, e.g., Cl, Br or I, or a sulfonyloxy group, e.g., tosyloxy or methanesulfonyloxy to produce a compound of the formula 7:

10



15 This reaction is run in the presence of a strong base M^+L^- such as NaH, KH, or potassium tertiary butoxide. The reaction may be performed at temperatures of from about - 78°C to about 100°C and may be run neat or in an inert solvent such as THF, DMF, etc.

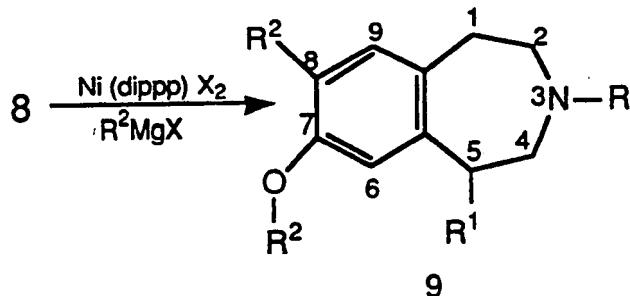
20 A compound of formula 7 may be reacted with a suitable reducing agent e.g. diborane or lithium aluminum hydride to reduce the carbonyl oxygen of the amide moiety and produce a compound of formula 8:



Suitable reducing agents include BH_3/THF , LiAlH_4 , $\text{NaBH}_4/\text{pyridine}$, and $\text{NaAlH}_2(\text{OC}_2\text{H}_5)_2$. The reaction may be performed at any suitable temperature, e.g. from about 0°C to about 5 120°C , and may be performed in an inert aprotic solvent such as THF or ether.

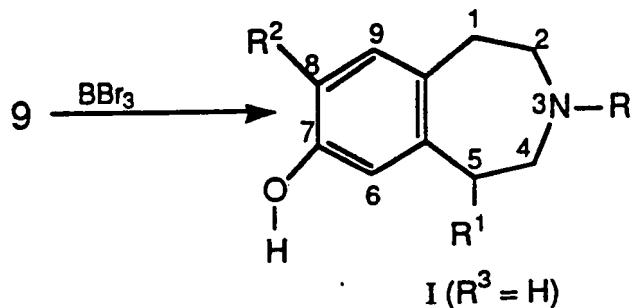
The 8-halo substituent in compound of formula 8 may be converted into a 8-($\text{C}_1\text{-}\text{C}_4$)alkyl substituent by reaction of compound 8 with a suitable alkylating reagent to produce a compound of formula 9:

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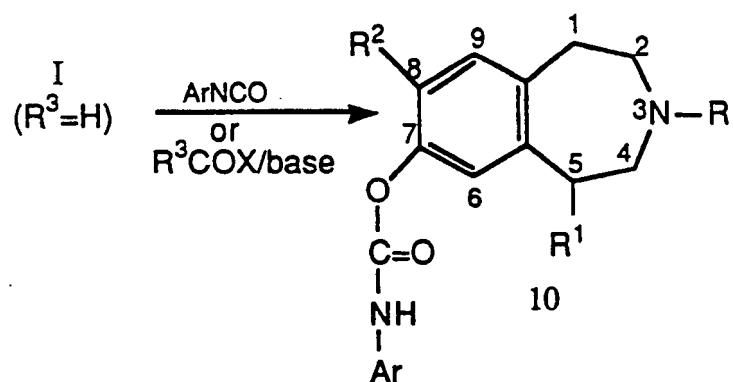
Suitable alkylating reagents include $\text{Ni}(\text{dppp})\text{X}_2/\text{R}^2\text{MgX}$. Nickel (II) diphenylphosphinopropane dichloride and CH_3MgX are preferred reagents. The reaction is performed in aprotic solvents such as THF, dioxane or ether at any suitable temperature, e.g. from about 15 0°C to about 120°C under anhydrous conditions and inert atmosphere, e.g., N_2 or argon.

The compound of formula 9 may be converted into 20 compounds of formula I wherein R^3 is H by reacting compound 9 with BBr_3 /ether or RSNa^+ in an appropriate non-aqueous aprotic solvent e.g. DMF to provide compounds of formula I:

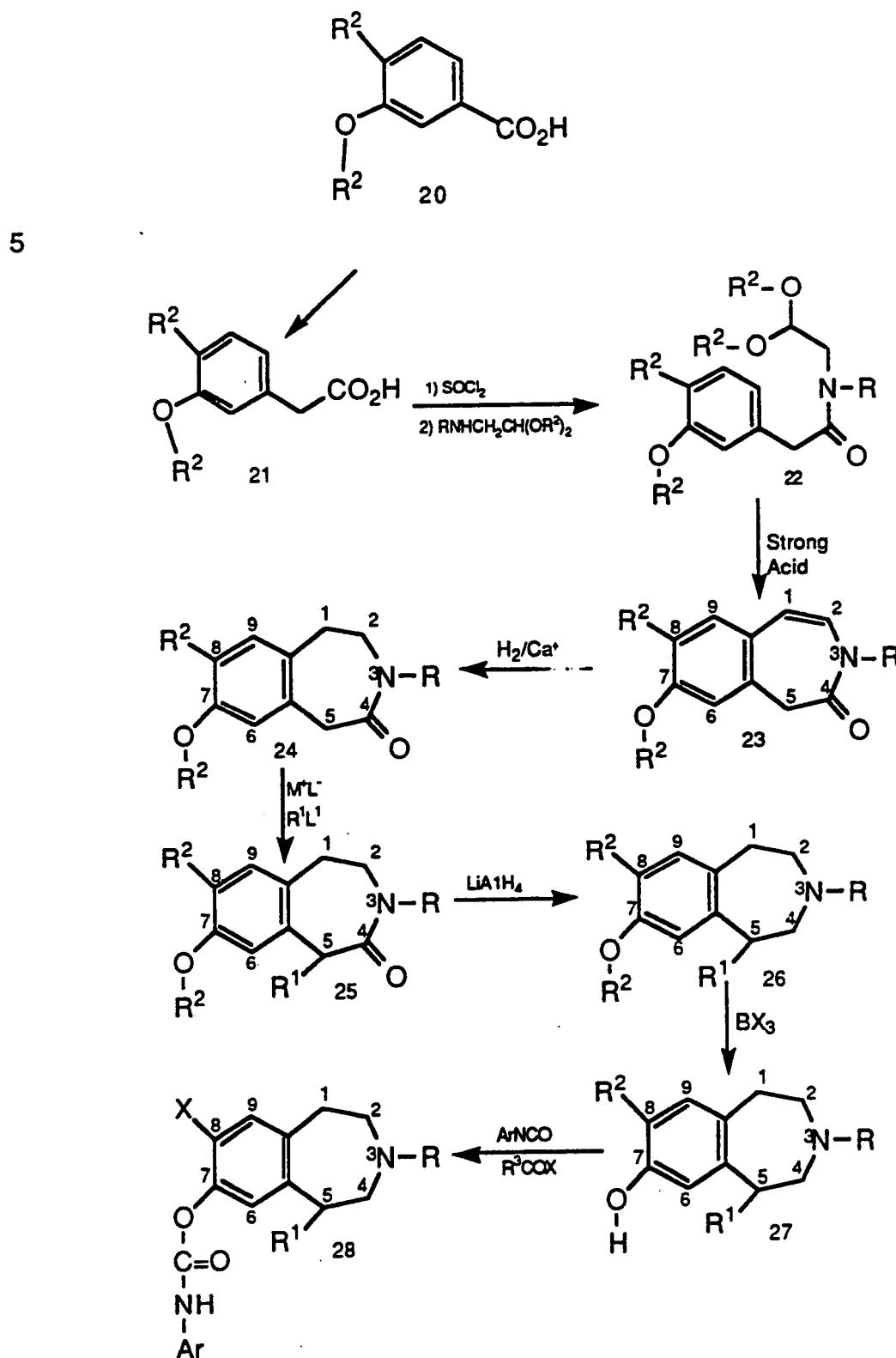


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The compounds of formula 10 may be prepared by reaction of compounds of formula I ($\text{R}^3=\text{H}$) with ArNCO or $\text{R}^3\text{COX}/\text{base}$:



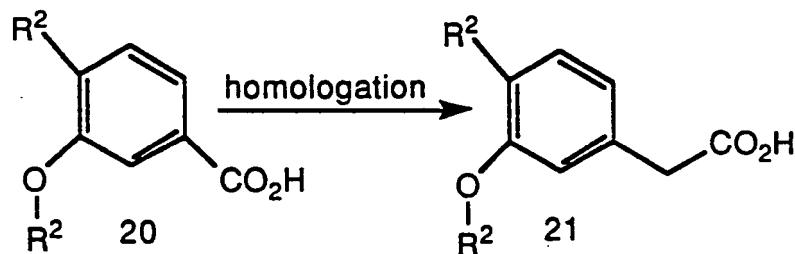
Any organic or inorganic base, e.g. pyridine or sodium
5 carbonate may be employed to react with the acid generated in this
reaction.

SCHEME B

The compounds of formula I may also be prepared by the sequence of steps illustrated in Scheme B.

The benzoic acids of formula 20 may be converted to the phenylacetic acids of formula 21 by the Arndt-Eistert synthesis (see Merck Index p. ONR-4, Tenth Edition, 1983).

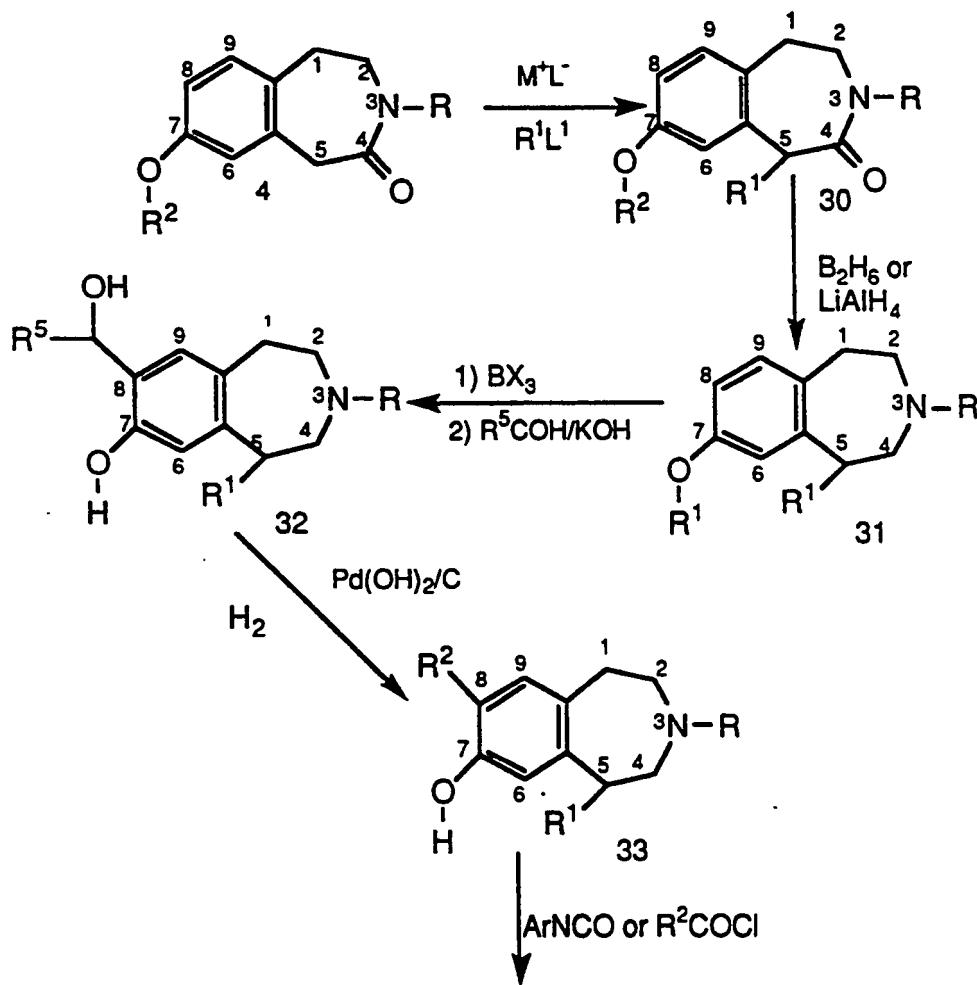
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The compounds of formula 20 are commercially available or may be prepared by standard synthesis techniques well known in the art. The series of steps outlined in Scheme B to convert compounds 21 into compounds 27 and 28 are exactly analogous to those outlined in Scheme A hereinabove.

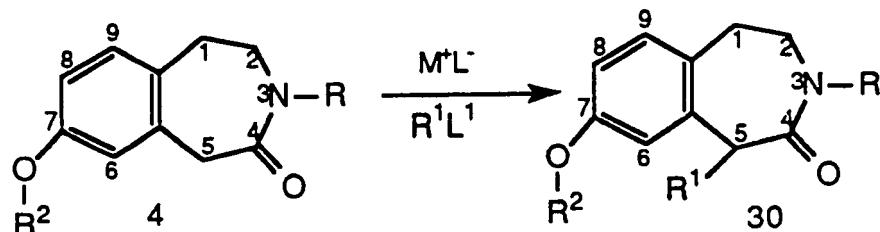
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SCHEME C



The compounds of formula I may also be prepared by using the sequence of steps illustrated in Scheme C.

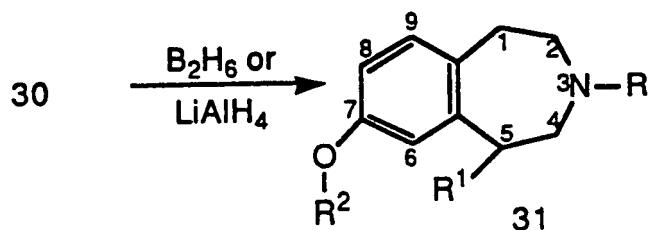
For example, the compounds of formula 4 (prepared as described in Scheme A) may be reacted in an electrophilic substitution reaction with a compound of formula R^1L^1 in the presence of strong base M^+L^- to produce a compound of formula 30



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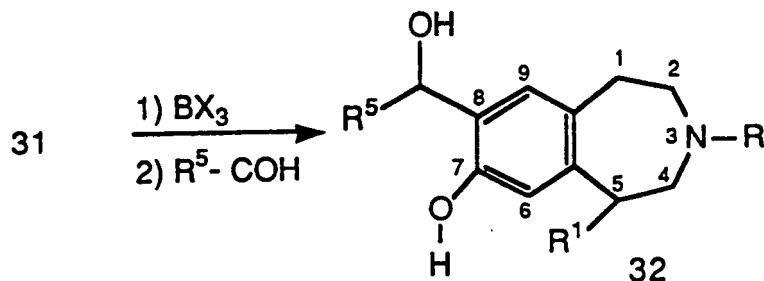
The reagents M^+L^- and R^1L^1 are as defined hereinabove in reference to production of compounds 7 from 6 in Scheme A.

A compound of formula 30 may be reacted with a suitable reducing agent e.g. diborane or lithium aluminum hydride to reduce the carbonyl oxygen of the amide moiety in 30 to produce a compound of formula 31:



20

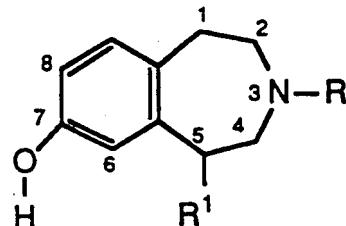
A compound of formula 31 may be reacted with BX_3 wherein X is Br, Cl or F, e.g. BBr_3 and thereafter with R^5-COH/KOH to produce a compound of formula 32:



25

The reaction with BBr_3 is normally run in an anhydrous aprotic solvent e.g., CH_2Cl_2 at room temperature overnight to produce the phenol formula of 31a:

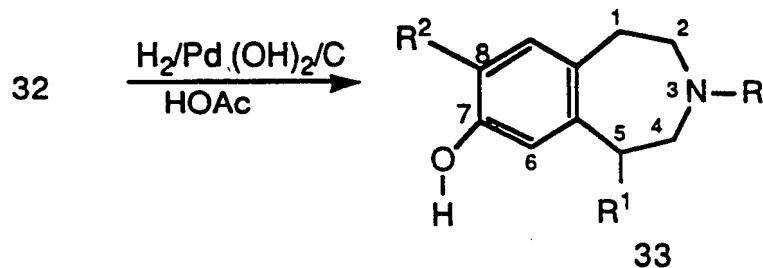
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31a

The phenol 31a is reacted with aldehyde R^5-COH , eg CH_2O in the presence of aqueous alkali metal hydroxide, e.g. 5% KOH
10 in water at 20 to 100°C preferably about 80° normally phenol 31a is dissolved in an inert solvent such as THF or DMF. R^5 in R^5-COH may be H or (C_1-C_3) alkyl

A compound of formula 32 may be reacted with a reducing agent, e.g. hydrogen/ $Pd(OH)_2$ on charcoal in acetic acid (HOAc) as
15 solvent to produce a compound of formula 33.



Normally a strong acid such as toluene sulfonic acid is
20 added to palladium II hydroxide on carbon in acetic acid and the reduction is run under elevated hydrogen pressure (50-60 psi) in any suitable hydrogenation apparatus at room temperature, overnight.

The phenol of formula 33 may be used as the free base, converted into the hydrogen chloride addition salt or compounds of
25 formula 10 by use of the procedures described in Scheme A for preparation of compound of formula 10 from 9.

The utility of the compounds of formula I may be demonstrated by the following test procedures designed to indicate their anti-psychotic and anti-depressive activity.

CONDITIONED AVOIDANCE SUPPRESSION (CAR) IN RATS

Clinically active antipsychotic drugs are known to depress discrete trial avoidance behavior at doses that do not retard escape response [Ann. N. Y. Acad. Sci. 66, 740 (1957)]. A series of experiments were carried out to assess the ability of the compounds of this invention to suppress the conditioned avoidance response (CAR) in rats.

10 Materials and Methods

Rats were required to jump onto a platform located 6.75 inches (17.15 cm) above the grid floor of an experimental chamber in response to a 5-second tone to avoid a 10-second foot shock (0.6 ma). Each experimental session consisted of 20 such trials presented at 30-second intervals. A correct CAR is scored whenever the rat jumps onto the platform during the tone (prior to foot shock). An escape response is scored when the rat jumps onto the platform during a shock. A response failure is defined as the lack of an escape response during the 10-second shock period.

20 Groups of 6-8 rats were trained in two consecutive days (total of 40 trials). Rats that reached criterion on day 2 (correct CARs on 16 or more of the 20 trials) were treated with either a test drug or vehicle on day 3. Suppression of CAR was analyzed statistically using Student's t-test comparing the performances of drug-treated to vehicle-treated rats. The minimal effective dose (MED) for each drug is defined as the lowest dose tested that significantly ($P<0.05$) reduced avoidance responding.

SQUIRREL MONKEY CONDITIONED AVOIDANCE

30 RESPONSE (CAR) TEST

This test was designed to measure the effective duration of candidate compounds.

Male or female squirrel monkeys weighing 800- 1200 g housed one per cage were utilized. Initially each monkey was taught to terminate a 3mA electric shock delivered through the grid floor of the test cage and an overlapping tone by depressing a lever in the cage. The monkeys did not proceed to the second phase of testing unless they depressed the lever during the shock component of the trials at least 75% of the time during 60 daily trials on three consecutive days.

In the second phase of the testing, a ten second tone is turned on prior to the shock component. A lever press during the sounding of the tone terminates the tone and prevents the occurrence of 5 the shock component and is denoted as an "avoidance". Compound testing does not begin until the monkey makes at least 85% correct avoidances for five consecutive days.

The compound testing was commenced after three consecutive days of re-testing. The monkey first was injected or orally 10 dosed with the vehicle only and retested to show that the vehicle does not affect the response of the monkey. The monkey must achieve at least an 85% correct avoidance before drug testing commences. If this minimal avoidance level is achieved, the next day the monkey is orally dosed or injected with the subject compounds in the appropriate vehicle 15 and the number of avoidances are recorded. An animal is defined as having been "affected" by any drug treatment if there is a 50% loss of avoidance behavior relative to the performance of the animal when only the vehicle was injected. The minimal effective dose (MED) is defined as that dose producing an effect in at least 50% of the animals.

20

RESULTS

A test was conducted to determine the effective duration of a compound of the present invention, (\pm)-5-(cyclohex-2'-en-1'-yl)-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol as a mixture of 25 diastereomers, denoted as Compound A, compared to a known compound, (d)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine maleate also named (+)-8-chloro-2,3,4,5-tetrahydro-5-phenyl-3-methyl-1H-3-benzazepin-7-ol maleate denoted as Compound B (Sch 23390).

30 It was determined that the ED₅₀ (approximately 5.6 mg/kg, po) of Compound A administered 60 minutes prior to the test was roughly equivalent to the ED₅₀ (2.4 mg/kg po) of compound B administered 30 minutes prior to test. The duration of each compound was determined by administering 5 X the po acute CAR inhibitory dose 35 of each (30 mg/kg of Compound, 10 mg/kg of Compound B) six hours prior to testing. The ability to significantly decrease the number of avoidances six hours after injection was used to indicate that the compound was still active at that time. The tests showed that

Compound A caused a significant decrease in the number 40 of avoidances ($p \leq 0.05$) whereas Compound B was inactive at that time.

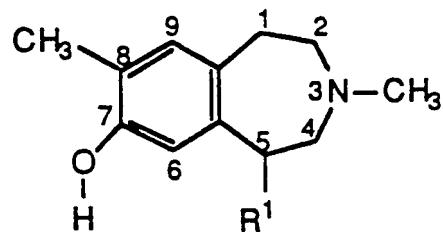
These results are presented below in Table II where N is the number of monkeys tested.

TABLE II

<u>TREATMENT</u>	DOSE (p.o.) <u>(mg/kg)</u>	N	MEAN (+SE) NUMBER OF AVOIDANCES AT 6 HOURS POST-
			<u>TREATMENT</u>
Vehicle	-	7	59.1 ± 0.9
Compound A	30	3	1.7 ± 1.7
Compound B	10	3	59.7 ± 0.3

Results

Representative compounds of the invention when tested by the above procedure manifested a dose-related specific blockade of conditioned avoidance response as set forth in Table III below:

TABLE III

Compound	R ¹	CAR				Duration (Monkey)	
		Rat		Monkey		po ¹	sc ¹
		po ¹	sc ¹	po ¹	sc ¹		
1	(±)-cyclohexyl	30	3	5.6	-	28	6h
2	(-)-cyclohexyl	>30	-	10	-	28	6h
3	(+)-cyclohexyl	17.8	-	5.6	-	28	6h
4	(±)-cyclopentyl	30	-	3	-	10 6h, 57 6h (Rat)	
5	(-)-cyclopentyl	-	-	-	-		
6	(+)-cyclopentyl	-	-	-	-		
7	(±)-2-cyclohexenyl (Isomers A+B)	10	-	5.6	-	30	6h
8	(±)-2-cyclopentenyl (Isomers A+B)	30	-	5.6	-	>18	6h
9	(±)-2-cyclohexenyl (Isomer A)	30	-	3	-	6h	15 mpk
10	(±)-2-cyclohexenyl (Isomer B)	30	-	3	-	15	6h
11	(±)-3-cyclopentenyl	-	-	-	-		
12	(-)-2-cyclohexenyl (Isomer A)	-	-	-	-		
13	(+)-2-cyclohexenyl (Isomer A)	-	-	-	-		
14	(-)-2-cyclohexenyl (Isomer B)	-	-	-	-		
15	(+)-2-cyclohexenyl	-	-	-	-		
16	(±)-2,4,6-cyclo- heptatrienyl	-	-	-	-		
17	(±)-1-cyclohexenyl	>30	-	3	-	10	1h

COMPETITIVE INHIBITION ASSAY

Many compounds capable of effecting reproducible

- 5 physiological changes in neural tissues are believed to operate by
binding at one or more receptor sites. Compounds which interact
strongly with these receptor sites in *in vitro* tests, using homogenates of
the target organ or structure, are expected to exhibit similar properties
when administered *in vivo* and are, therefore, candidates for continued
10 study as potential therapeutic and/or diagnostic agents.

Binding of a compound to a receptor site, *in vitro*, is
demonstrated by the specificity of binding and the saturability of the
available sites. A methodology for characterization of binding and an
interpretation of the data are described by Billard et al., Life Sciences
15 35, 1885 (1984) in which the binding of the benzazepine (R)- (+)-8-
chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1H-3-benzazepin-7-ol
hemimaleate (SCH 23390) to the dopamine D-1 receptor is
characterized.

20 Materials and Methods

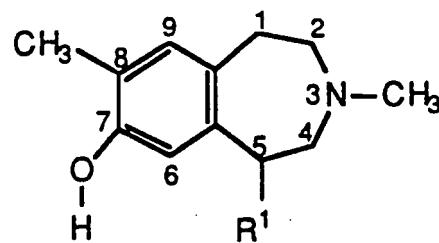
Tritiated SCH 23390 and tritiated spiperone (a potent D-2
ligand) were obtained as described in the Billard et al. reference supra
and serially diluted in 0.05 M Tris buffer, pH 7.4, as required. A
compound of the invention is diluted in 0.05 M Tris buffer, pH 7.4, as
25 required.

Tissue Preparation

Male Sprague-Dawley rats (200 to 250 g) from Charles
River Breeding Laboratories, Mass. were used to obtain brain tissue.
30 The rats were humanely sacrificed and their brains removed and placed
on ice. Striatal tissue was excised, pooled, and homogenized
(Brinkman Polytron, 10 sec) in 100 volumes (w/v) of ice cold 50 mM Tris
buffer, pH 7.4 (at 25°C). The homogenate was centrifuged at 20,000 xg
for 10 min. The resultant pellet was rehomogenized in Tris buffer and
35 centrifuged again. The final pellet was resuspended in 50 mM Tris
buffer, pH 7.4 containing 120 mM NaCl, 5 mM KCl, 2 mM CaCl₂, and 1
mM MgCl₂.

Assay

Polypropylene incubation tubes received 100 μ l of the individual test compounds at various concentrations dissolved or suspended in 0.05 M Tris buffer, pH 7.4 containing 4 mg/ml methylcellulose, 100 μ l of a solution of 3 H-SCH 23390 in Tris buffer (final reaction mixture concentration =0.3 nM) or 100 μ l of a solution of 3 H-spiperone in Tris buffer (final concentration =0.2 nM) and 800 μ l of tissue suspension (ca. 3 mg/assay). Tubes were incubated at 37°C for 15 minutes and rapidly vacuum filtered through Whatman GF/B filters and rinsed 4 times with 4 ml of ice cold 50 mM Tris buffer, pH 7.4. The filters were transferred to scintillation vials, equilibrated with 10 ml of scintillant (Scintosol, Isolab, Inc.) for 16 hours at 25°C and the radioactivity determined in a liquid scintillation counter. K_i values were determined as described by Billard et al. using the relationship $K_i = IC_{50}/(1 + ([L]/K_D))$ wherein IC_{50} =concentration of test drug necessary to displace 50% of specifically bound 3 H-Sch 23390, [L]=concentration of radioligand used in the assay, and K_D =dissociation constant.

TABLE IV

5

<u>Compound</u>	<u>R¹</u>	<u>³H-Sch 23390</u>	<u>K₁</u> —(nM) ₃
			<u>³H-Spiperone</u>
1	(±)-cyclohexyl	48	3606
2	(-)-cyclohexyl	22	2051
3	(+)-cyclohexyl	68	2902
4	(±)-cyclopentyl	68	2903
5	(-)-cyclopentyl	44	1055
6	(+)-cyclopentyl	90	6058
7	(±)-2-cyclohexenyl (Isomers A+B)	10	735
8	(±)-2-cyclopentenyl (Isomers A+B)	36	1159
9	(±)-2-cyclohexenyl (Isomer A)	18	1215
10	(±)-2-cyclohexenyl (Isomer B)	6	438
11	(±)-3-cyclopentenyl	31	1067
12	(-)-2-cyclohexenyl (Isomer A)	13.5	780
13	(+)-2-cyclohexenyl (Isomer A)	30.5	3044
14	(-)-2-cyclohexenyl (Isomer B)	4	240
15	(+)-2-cyclohexenyl (Isomer B)	41	2545
16	(±)-2,4,6-cyclo- heptatrienyl	27.3	2462
17	±-(1)-cyclohexenyl	8.76	1876

Result

The inhibition constants (K_i) determined from the assays for compounds of the invention are as shown in Table IV below.

5 The comparatively small K_i values of these compounds in the competitive binding assay with SCH 23390 indicate that the compounds of formula I bind strongly to the D-1 receptor site. The relatively high K_i values for the D-2 site, for which spiperone is highly selective, indicates that the compounds are not specifically bound to that
10 receptor site.

15 The antidepressive method of the invention is identified, for example, by test procedures which measure a compound's effect on tetrabenazine (TBZ)-induced ptosis in mice or which measure a compound's effect on muricide activity in rats as discussed below.

ANTIDEPRESSANT POTENTIALEFFECTS ON TETRABENAZINE (TBZ)-INDUCED PTOSIS
IN MICE

20 Clinically active antidepressant drugs are known to block TBZ-induced ptosis in mice (Psychosomatic Medicine, Nodine and Moyer, Eds., Lea and Febiger, Philadelphia, 1962, pp 683-90). Activity in this test is used to predict anti-depressant activity in man.

Methods and Materials

25 Groups of 5 mice are administered test drugs followed 30 minutes later by ip injection of tetrabenazine, 30 mg/kg. Thirty minutes later, the degree of ptosis is evaluated. Percent blockade of each treated group is used to determine ED_{50} 's, defined as that dose which
30 prevents ptosis in 50% of mice. ED_{50} 's and 95% confidence limits are calculated by probit analysis.

EFFECTS ON MURICIDAL BEHAVIOR IN RATS

Blockade of muricidal (mouse-killing) behavior in rats is
35 used as a measure of evaluating the anti-depressant activity of drugs (Int. J. Neuropharmacol., 5, 405-11 (1966)).

Methods and Materials

Groups of 5 rats are administered test drug intraperitonially and are tested 30 and 60 minutes later for presence of muricidal behavior. Percent blockade of each treated group using data obtained at both these time points is calculated and dose-response data are used to determine each ED₅₀. ED₅₀ is defined as that dose which blocks muricide behavior in 50% of treated rats and is calculated using probit analysis.

The analgesic effect of the compounds of formula I and the method for providing analgesia may be exemplified by the Acetic Acid Writhing Test in Mice described below.

ACETIC ACID WRITHING TEST IN MICE

The blockade of writhing induced by the intraperitoneal injection of acetic acid is an established experimental animal model for the screening of antinociceptive drugs (drugs which prevent the appreciation or transmission of pain sensations). See Hendershot et al., J. Pharmacol. Exp. Therap. 125:237, (1959) and Koster et al., Fed. Proc. 18:412, (1959).

METHODS AND MATERIALS

Compounds to be tested are dissolved or suspended in aqueous 0.4% methylcellulose vehicle. For oral administration, dosages are prepared for delivery of the selected weight of compound in a total volume of 20 mg/kg of body weight. For subcutaneous or intraperitoneal administration, dosages are prepared for delivery of the selected weight of compound in a volume of 10 ml/kg of body weight.

The test procedure is that described by Hendershot et al., supra, except that acetic acid is substituted for phenylquinone. Groups of five male CF1 mice (20-26 g.) are dosed orally with test drug and injected 15 minutes later with 0.6% aqueous acetic acid (10 mg/kg). The mice are placed in a large observation beaker and the number of writhes for each animal is counted during a 10 minute interval starting 3 minutes after injection of acetic acid. A writhe is defined as a sequence of arching of the back, pelvic rotation and hindlimb extension. Initial screening is performed using a dosage of 30 mg/kg. If this dose affords 50% or greater reduction in the number of writhes compared to the control, the animal is considered to be protected, a dose response curve is developed using a logarithmic sequence of lower doses and an

ED_{50} is determined by interpolation.

Regarding toxicity, the compounds of this invention are non-toxic at the therapeutic dose.

5 For preparing pharmaceutical compositions from the compounds of formula I, inert, pharmaceutically acceptable carriers are admixed with the active compounds. The pharmaceutically acceptable carriers may be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and
10 suppositories. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegrating agents; it may also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In
15 the tablet, the active compound is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets typically contain from 5 to about 70% of the active ingredient dependent upon the potency of the active compound, the size and age of the intended user,
20 and the range of dosage required for the specific therapy. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and other materials typically used in the pharmaceutical industry. The term
25 "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier, providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. Similarly, cachets are included. Tablets, powders, cachets and capsules can be
30 used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by

adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by
5 dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations
10 for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions. These particular solid form preparations are most conveniently provided in unit dose form and as such are used to provide a single liquid dosage unit. Alternatively, sufficient solid may be provided so that after conversion to liquid form,
15 multiple individual liquid doses may be obtained by measuring predetermined volumes of the liquid form preparation as with a syringe, teaspoon or other volumetric container. The solid form preparations intended to be converted to liquid form may contain, in addition to the active material, flavorants, colorants, stabilizers, buffers, artificial and
20 natural sweetners, dispersants, thickeners, solubilizing agents and the like. The solvent utilized for preparing the liquid form preparation may be water, isotonic aqueous salt solutions, ethanol, glycerine, propylene glycol and the like, as well as mixtures thereof. The solvent utilized will be chosen with regard to the route of administration. For example, liquid
25 preparations containing large amounts of ethanol are not generally suitable for parenteral use.

The invention also contemplates alternative delivery systems including, but not necessarily limited to, transdermal delivery. The transdermal compositions can take the form of creams, lotions
30 and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active components. The unit
35 dosage form can be a packaged preparation, the package containing discrete quantities of preparation such as packeted tablets, capsules and powders in vials or ampules. The unit dosage form can also be a capsule, cachet or tablet itself, or it may be the appropriate number of any of these in a packaged form.

The quantity of active compound in a unit dose preparation may be varied or adjusted from 1 mg to 100 mg according to the particular application and the potency of the active ingredient and the intended treatment. A dose of about 0.02 to about 2.0 mg/kg, preferably about 0.02 to about 0.2 mg/kg, may be employed and may be divided over 1 to 3 administrations per day. The composition may, if desired, also contain other therapeutic agents.

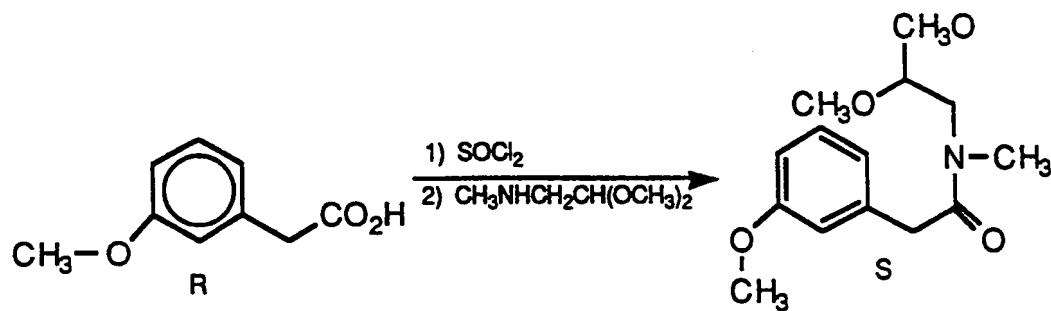
The dosages may be varied depending on the requirement of the patient, the severity of the condition being treating and the particular compound being employed. Determination of the proper dosage for a particular situation is within the skill of those in the medical art. For convenience, the total daily dosage may be divided and administered in portions throughout the day or by means providing continuous delivery.

The invention disclosed herein is exemplified by the following examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of applicants' invention may be apparent to those skilled in the art.

EXAMPLE 1

Step A

25



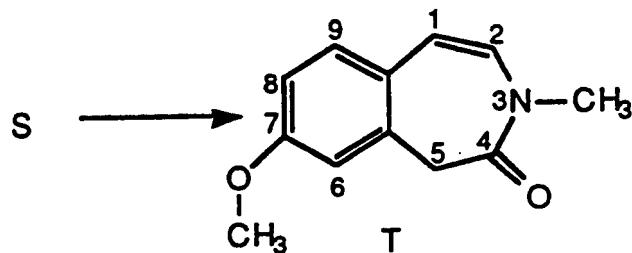
85 ml of thionyl chloride was added dropwise to a solution of 64.0 g of the acid of formula R above in 100 ml of dry dichloromethane with stirring. The mixture was stirred at room temperature for 3 hours longer and then heated on a steam bath under gentle refluxing for two hours. The low boiling material (solvent and excess SOCl_2) was distilled off at about 50°C under vacuum. The

residue was dried under vacuum at room temperature for 2 hours longer.

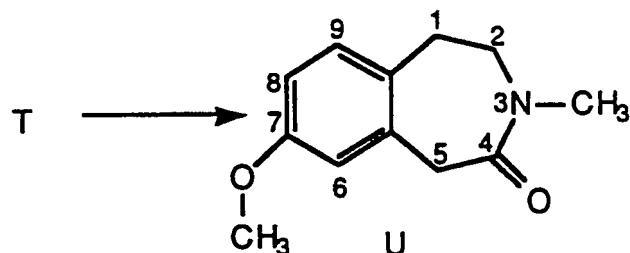
The concentrated acid chloride produced was dissolved in
 5 120 ml of CH_2Cl_2 and then added dropwise to a stirring solution of 50 ml of N-methylaminoacetaldehyde dimethylacetal and 80 ml of triethylamine (50% excess) in 350 ml of methylene chloride for 1.5 hours at 20-25°C with occassional cooling. The mixture was stirred at room temperature for one hour longer. The reaction mixture was extracted
 10 twice with 500 ml of water, dried over MgSO_4 , filtered and then rotovaporated down to dryness to provide about 100 g of the compound of formula S above as a viscous syrup.

Step B

15



The viscous syrup was added in small portions to 500 ml of $\text{CH}_3\text{SO}_3\text{H}$ (previously chilled in an ice bath) with cooling and stirring (ice bath). This was further diluted with 500 ml of acetic acid. The mixture was stirred at room temperature overnight. The reaction mixture was poured into 8 liters of ice and H_2O with stirring over 30 minutes. A gummy solid was filtered off and washed with water. The filtrate was extracted with one liter of CH_2Cl_2 and rotovaporated down to dryness.
 20 25 The residue of the rotovaporation and the wet gummy solid were combined and redissolved in 700 ml of ether. The ether was extracted twice with 300 ml of water, and the ether solution was dried over K_2CO_3 , charcoal, filtered and then rotovaporated down to dryness to provide 68.0 g of a viscous syrup which crystallized out upon seeding to give the
 30 compound of formula T above.

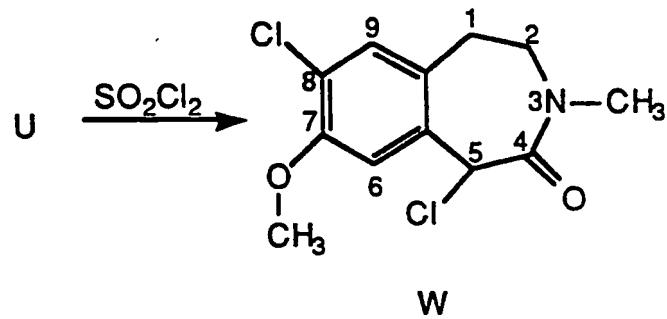
Step C

5

68.0 g of the material of formula T from Example 1B above were dissolved in 600 ml of ethanol which was then divided into two equal portions and each portion was reduced with H_2 over 2.5 g of PtO_2 .

After removing the catalyst, the filtrates of both runs were
10 combined, checked with TLC and roto-evaporated down to dryness. The residue was stirred with 150 ml of cold ethyl acetate with seeding. The solution was chilled in an ice bath, filtered and the solid was washed with cold ethyl acetate to provide about 28.0 g of the compound of formula U. 24.0 g of this material and 12.0 g from another batch were
15 combined and dissolved in 100 ml of boiling ethyl acetate. The mixture was cooled in a freezer and filtered, and the solid was washed with cold ethyl acetate. The solid was dried at room temperature for one hour to provide 22.50 g of the compound of formula U, m.p. 104-105°C.

20

Step D

To a solution of the compound of formula U above in 300
25 ml of CH_2Cl_2 was added a solution of 15 ml of SO_2Cl_2 in 35 ml of CH_2Cl_2 in a period of about 25 minutes. The reaction mixture was stirred at room temperature for 2 1/2 hours longer and poured into 500 ml of ice water with stirring. The organic layer was dried over MgSO_4 ,

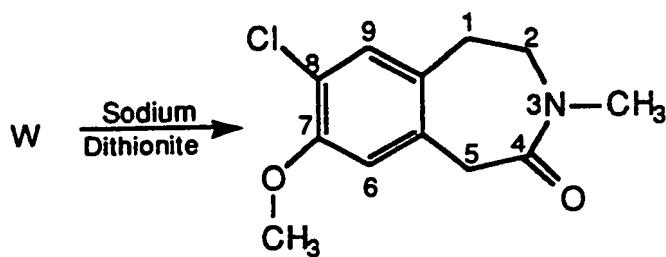
filtered and then rotovaporated down to dryness. The residue crystallized out partially. The mixture was then triturated with 40 ml of cold ethyl acetate and filtered, and the solid which separated was 5 washed with 10 ml of cold ethyl acetate to provide 13.90 g of the compound of formula W, m.p. 162-164°C.

The filtrate was kept in a freezer overnight and then filtered to provide an additional 1.20 g of the compound of formula W of lesser purity.

10

EXAMPLE 2

Step A

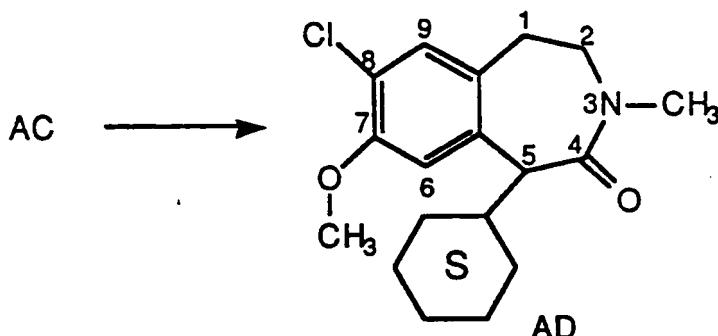


15

A mixture of 1.40 g of the compound of formula W, prepared as described in Example 1D, 4.0 g of NaHCO_3 and 1.75 g of sodium dithionite in 20 ml each of DMF and H_2O was stirred at room

20 temperature for 1 1/2 hours. 200 ml of water were added with stirring. The mixture was filtered and the solid separated was washed with water to provide about 1.09 g of solid, which was recrystallized from acetonitrile to provide a small amount of the desired compound of formula AC, m.p. 117-118°C. The filtrate from the acetonitrile recrystallization provided 950 mg of less pure compound of formula AC.

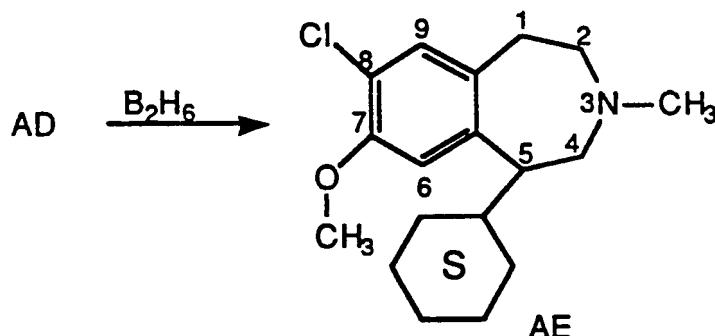
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Step B

- 5 Under N_2 , NaH (876 mg, 60% oil dispersion) was added to a solution of the compound of formula AC (2.5 g) in 150 ml of THF/DMF (10:1) at room temperature. A solution of cyclohexyl bromide (1.5 cc) in THF/DMF (10 cc) was added via dropping funnel to the above mixture. The mixture was heated on an oil bath at 80°C. After 2 hours the
 10 reaction was complete. Solvent was removed on a rotovap at 40°C (vac. pump associated) and the residue was diluted rapidly with 200 cc of ice water. The resulting mixture was extracted with 200 ml of CH_2Cl_2 and the CH_2Cl_2 layer was separated and dried over $MgSO_4$. Rotovaporation of the CH_2Cl_2 layer gave 3 g of amorphous solid which
 15 was chromatographed on Kieselgel 60G using ethyl acetate/hexane (40:60) as the eluant to give about 1.54 g of the product of formula AD.

EXAMPLE 3

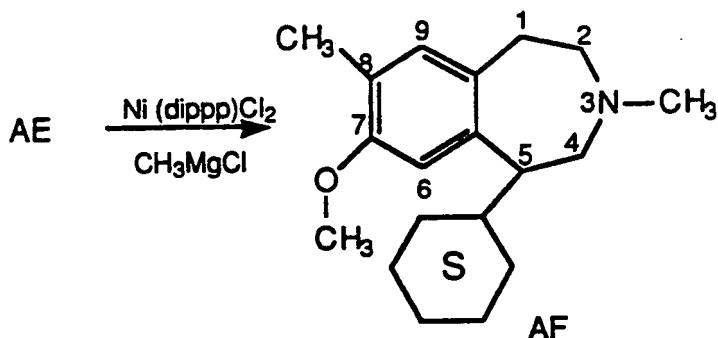
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Step A

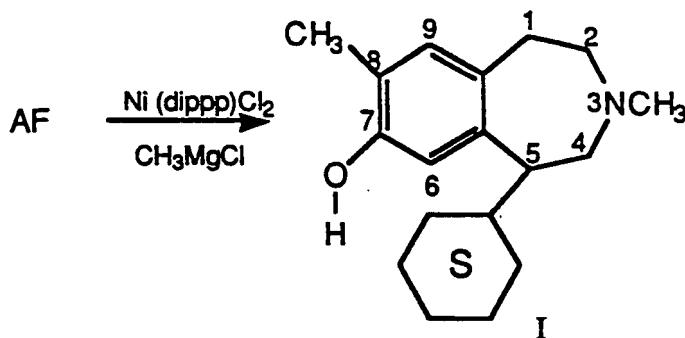
- The compound of formula AD (1.53 g), prepared as
 25 described in Example 2B, dry THF (50 cc) and diborane (16 cc of a 1 M solution in THF) were refluxed for 2 hrs. The reaction mixture was cooled to room temperature and 5 cc of H_2O was added carefully.

Solvent was removed on a rotovap at about 30°C. Ethanol (100 cc) and 25 cc of 4N HCl were added to the residue, and this mixture refluxed on a steam bath for 1 1/2 hours. Ethanol was removed on a rotovap at 50-60°C. and the remaining aqueous portion was diluted with 100 ml of ice water. The mixture was basified with 10% NaOH solution to a pH of about 8 and extracted twice with 100 cc portions of CH₂Cl₂. The combined extracts were dried over MgSO₄, and evaporated to give 1.26 g of the compound of formula AE above as an oil.

Step B



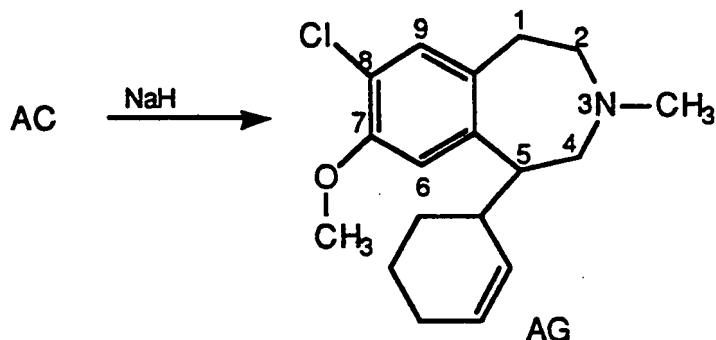
To a solution of the compound of formula AE (5.10 g) and 1.0g of Ni (II) diphenylphosphinopropane dichloride, Ni(dipppe)Cl₂, in 100 mL of dry dioxane, under N₂, in a flask immersed in an ice bath, add, with stirring, 20 mL of 3M CH₃MgBr in diethyl ether. Stir the so-formed reaction mixture at a temperature of 100°C under N₂ overnight. Rotoevaporate the solvents and treat resultant dry residue (with cooling) with 120 mL of saturated NH₄Cl solution. Extract the so-formed aqueous mixture with diethyl ether (2x100 mL) and dry the combined organic layer over K₂CO₃. Filter the dried layer and rotoevaporate the filtrate to give AF as an oily residue.

Step C

5 A solution of the cyclohexyl compound of formula AE above (1.2 g) in 6 ml of dimethylformamide (DMF) was added to a solution of sodium thioethoxide in 6 ml of DMF prepared from 757 mg of 60% sodium hydride in mineral oil and 1.4 ml of ethanethiol. The resulting mixture was heated at 120°C on an oil bath for 4 hrs, cooled,
 10 diluted with 100 ml of ice-water, and washed with 50 ml of hexane. 5% HCl was added to the separated aqueous layer to adjust the pH to 7.5-8. The mixture was extracted twice with 200 ml portions of CH_2Cl_2 , and the combined extracts were dried over MgSO_4 , filtered, and evaporated to give an oil which was dried in high vacuum. The oil partially crystallized
 15 and was recrystallized from ether-petroleum ether to give 454 mg product of the formula I: $\text{R}=\text{R}^2=\text{CH}_3$ $\text{R}^3=\text{H}$, $\text{R}^1=\text{cyclohexyl}$ above, m.p.
 144-147°C.

EXAMPLE 4

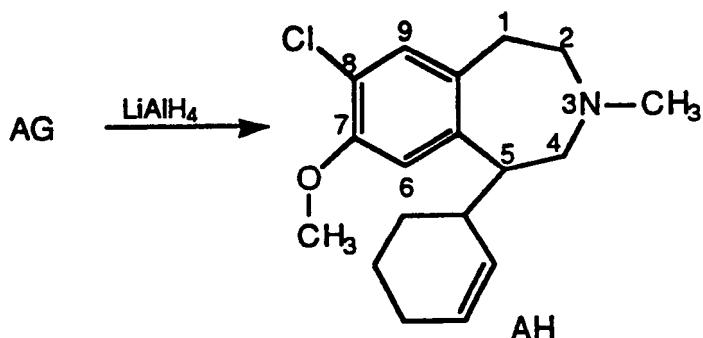
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Step A

25 Under an argon atmosphere, NaH (2.9g, 74 mmol, 60% oil dispersion) was added to a solution of formula AC prepared as

described in Example 2A (9.0g, 37.54 mmol) in 100 mL of THF/DMF (9:1, v/v) at 0°C. The so-formed reaction mixture was stirred at 0°C for 5 min and at room temperature for 20 min. A solution of 3-
 5 bromocyclohexene (6.1 ml, 37.0 mmol) in THF/DMF was added dropwise to the above reaction mixture. The temperature of the resultant reaction mixture was raised to 80°C and maintained thereat, with stirring for 2 1/2 h. The reaction mixture (which showed no starting material (AC) by TLC) was cooled to room temperature and then to 0°C.
 10 Water (50 mL) was slowly added thereto and the resultant mixture was warmed to room temperature. The THF was removed on a rotoevaporator and 150 mL of water was added to the resultant solution. The so-formed solution was extracted with ethyl acetate (3 x 100 mL) and the organic layer was separated, and dried over Na₂SO₄. The
 15 dried organic layer was filtered and rotoevaporated to dryness. The crude product was chromatographed on silica gel using ethyl acetate as the eluant to give about 10.2g (85% of theory) of the compound of formula AG. The ¹H NMR was consistent with the proposed structure of AG.
 20

Step B



25 To the compound of formula AG (12.0 g, 37.5 mmol) prepared in accordance with the procedure of step A of Example 4, in dry THF (500 mL) at 0°C, there was added lithium aluminum hydride (4.25g, 112.5 mmol), in several portions. The so-formed reaction mixture was stirred at 0°C for 10 min., room temperature for 10 min and thereafter at reflux for 2h. The resultant reaction mixture was cooled to 0°C and there was slowly added thereto, in sequence: 4 mL of water (dropwise), 5 mL of 10% NaOH and 5 mL of water. The so-formed mixture was stirred at room temperature for 1 hr. and thereafter filtered through Celite. The solvents were rotoevaporated and the crude
 30

product was chromatographed on silica gel eluting with ethyl acetate to give 9.2g (80% of theory) of the compound of formula AH. The ¹H NMR was consistent with proposed structure.

5

EXAMPLE 5

CHROMATOGRAPHIC SEPARATION OF COMPOUND AH INTO DIASTEREOISOMERS (±)-A and (±)-B

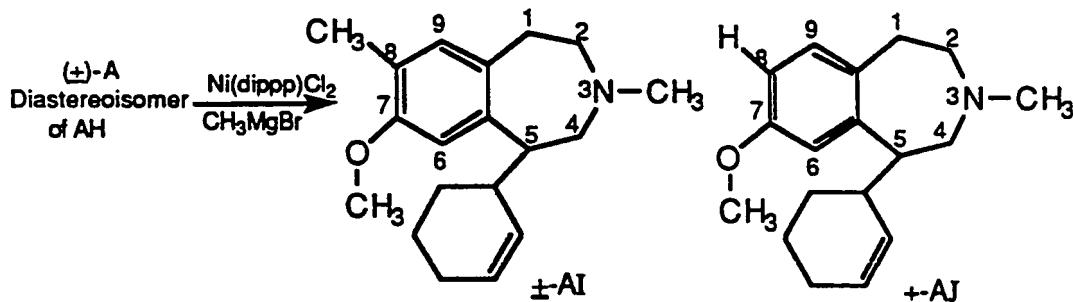
10 A solution of 5.0g of the crude compound of formula AH prepared in accordance with procedure of Example 4 in 50 mL of CH₂Cl₂ was added to a chromatography column packed with 350g of TLC grade silica gel. Fractions were collected using as eluant first with ethylacetate (ETOAC): CH₂Cl₂:NH₄OH (4:200:1.5) and then (10:200:15) (v/v/v). The fractions containing pure (±)-A by TLC, pure (±)-B by TLC and mixtures thereof were pooled and the solvents evaporated therefrom to provide 5.10g of (±)-A diastereoisomer, and 2.95g of pure (±)-B diastereoisomer

15

20

EXAMPLE 6

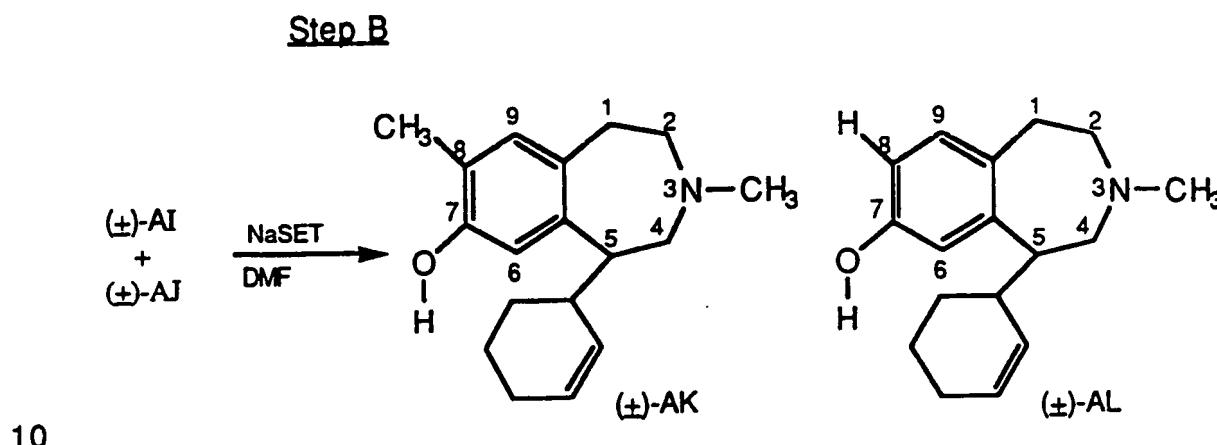
Step A



25

To a solution of the (±)-A diastereoisomer of the compound of formula AH, (6.50g) prepared and separated as described in Example 5, and 1.0g of Ni (II) diphenylphosphinopropane dichloride, 30 Ni(dipp)₂Cl₂, in 100 mL of dry dioxane, under N₂, in a flask immersed in an ice bath, there was added, with stirring, 20 mL of 3M CH₃MgBr in diethyl ether. The temperature of the stirred so-formed reaction mixture was slowly raised to 100°C and maintained thereat under N₂ overnight. The solvents were rotoevaporated and the resultant dry residue was

treated (with cooling) with 120 mL of saturated NH₄Cl solution. The so-formed aqueous mixture was extracted with diethyl ether (2x100 mL) and the combined organic layer was dried over K₂CO₃ and filtered. The solvent was rotovaporated to give 6.2g of an mixture of (+)-AI and (+)-AJ as an oily residue.



10

A solution of 6.20g of the crude mixture of (±)-AI and (±)-AJ from Step B, was stirring added to oil mole of NaSET (NaS C₂H₅) prepared from 4.0g of 60% NaH in mineral oil and 7.40 mL of ethanethiol in 60 mL of dry DMF under N₂. The temperature of the so-formed reaction mixture was raised to 140°C and maintained thereat, with stirring under N₂ for 6h. The reaction mixture was cooled, diluted with 100 mL of ice-water and washed with 50 mL of hexane. To the separated aqueous layer, there was added 50% HCl to adjust the pH to 7.5 to 8.0. The so-formed mixture was extracted with CH₂Cl₂ (2 x 200 mL) and the combined organic layers were dried over MgSO₄, filtered and rotovaporated to give 4.9g of a gum-like residue. The residue was chromatographed on 200g of TLC grade silica gel, eluting with CH₂Cl₂:EtOAc:NH₄OH (200:3:1, v/v/v). The fractions containing pure (±)-AK and (±)-AL were pooled to give 800 mg of the compound of formula (±)-AK (pure by TLC), and 1.40g of the compound of formula (±)-AK (slightly impure (>95% pure) by TLC).

EXAMPLE 7

30 RESOLUTION OF THE RACEMIC (+)-AK INTO (+)-AK and (-)-AK AS THE HYDROGEN CHLORIDE SALTS

A solution (±)-AK prepared in accordance with Example 6 dissolved in acetic acid (3g/L) was injected into a Rainin rabbit HPX

HPLC equipped with the following preparatory scale column: 41.4mm x 25cm Dynamax 83-543- C5,C_{4/5}) silica gel (300 pore size) having a Chiral Mobile Phase: 0.02M beta-cyclodextrin in 8% CH₃CN in water; 5 buffer to pH 5 with 0.05M KH₂PO₄; flow rate: 4.5 to 6 mL/min; pressure 900 psi; loading: 15 mg/per injection; UV detector. Collect fractions of pure (-)-AK (-)-AK rich, and (+)-A rich. Analysis was performed on HPLC using the above conditions with a 4.6 mm x 25 cm. Dynamax 83-303-C 10 C_{8/12}) silica gel analytical column. A NaOH solution was added to each of these three pooled fractions to adjust the pH to 8-9 and the so-formed mixtures were separately extracted with ethyl acetate. The solvent was rotoevaporated to give a sample of pure

(-)AK, a sample rich in (-)-AK and a sample rich in (+)-AK. The sample rich in (-)-AK was dissolved in HOAc and injected into the 15 preparatory HPLC column under the above conditions. The sample of pure (-)-AK was placed on preparatory TLC silica gel plates, developing the plates with CH₂Cl₂:MeOH:NH₄OH (50:7:1, v/v/v); extractant being MeOH. The pure sample of (-)-AK so-obtained dissolved in diethyl ether was added a solution of HCl (g) in diethyl ether until pH=3. The so- 20 formed solution was allowed to stand about 0.5h, and, the so-formed white precipitate was filtered and dried in vacuo to give 62 mg of (\pm)-AK·HCl as a white solid. The same procedure was followed to purify The impure sample of (-)-AK-rich and (+)-AK-rich to provide a total of 110 25 mg of pure (-)-AK·HCl as a white solid and 110 mg of (+)-AK·HCl as a white solid.

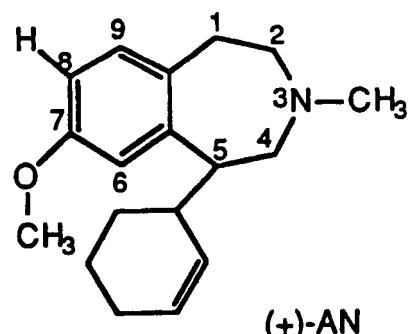
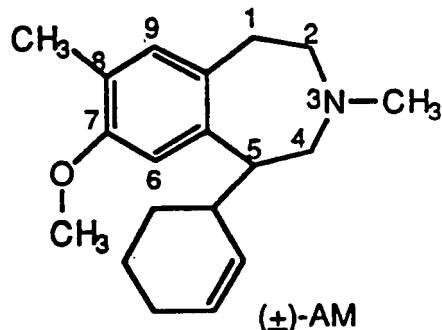
EXAMPLE 8

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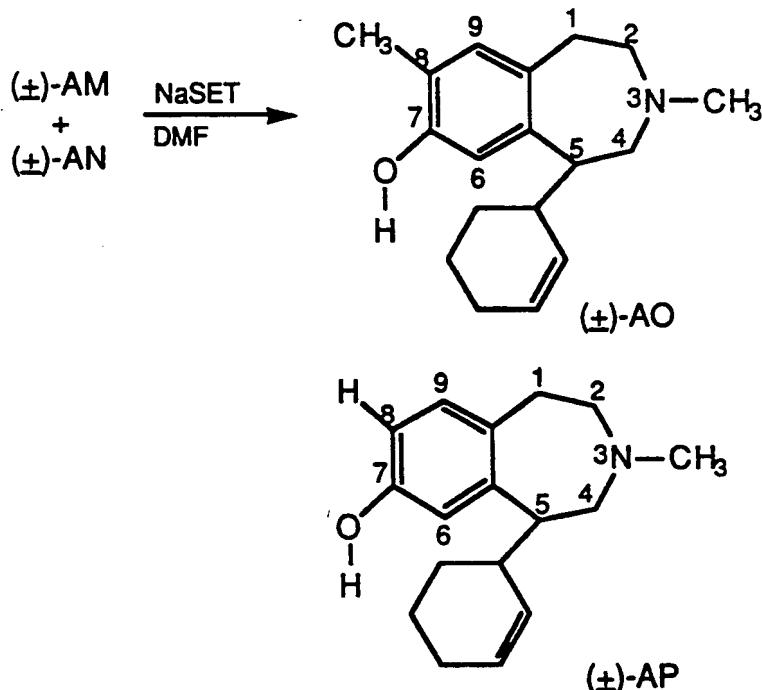
Step A

(\pm)-B Diastereoisomer
of (\pm)-AH

$\xrightarrow[\text{CH}_3\text{MgBr}]{\text{Ni (dipp)} \text{ Cl}_2}$



The procedure of Example 6, Step A was followed except
that an equivalent amount of the (\pm)-B diastereoisomer of (\pm)-AH
10 obtained from Example 5 was used to provide a mixture of (\pm)-AM and
(\pm)-AN.

Step B

5

The procedure of Example 6, Step B was followed except that an the mixture of $(\pm)\text{-AM}/(\pm)\text{-AN}$ from Step A of this Example was substituted for the mixture of $(\pm)\text{-AI}/(\pm)\text{-AJ}$ to provide the mixture of pure $(\pm)\text{-AO}$ and $(\pm)\text{-AP}$.

10

EXAMPLE 9

RESOLUTION OF THE MIXTURE OF RACEMIC (+)-AO INTO (-)-AO AND (+)-AO AS THE HYDROGEN CHLORIDE SALTS

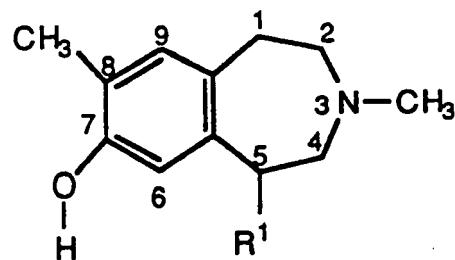
15

The procedure of Example 7 was followed except that the racemic mixture of $(\pm)\text{-AO}$ was used in place of $(\pm)\text{-AK}$ to obtain 15 mg of $(-)\text{AO}\cdot\text{HCl}$ as a white solid and 8 mg of $(+)\text{AO}\cdot\text{HCl}$ as a white solid.

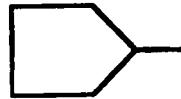
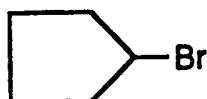
20

EXAMPLE 10

By employing the reactants tested in the left hand column of Table 3 herein below in place of 3- cyclohexenyl bromide used in Example H Step A and thereafter employing the procedure of Example 4, Step B and the appropriate separation procedures of Examples 5-9, the compounds listed in the right-hand column of Table V were obtained.

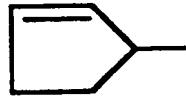
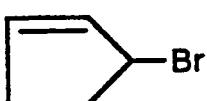
TABLE V

5

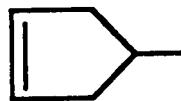
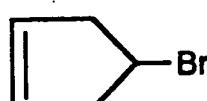
Reactant R_1 

as the racemate (\pm)
or as (+) and (enantiomers)

10

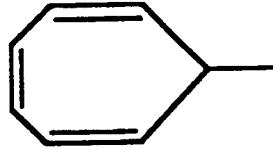
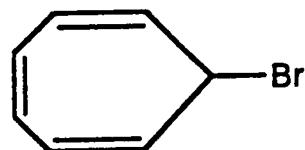


as the racemate (\pm)
and as (+) and (-)



as the racemate (\pm)

15



as the racemate (\pm)

Similar results would be expected for compounds wherein C₂-C₄ were used in the 8 position in place of CH₃.

20

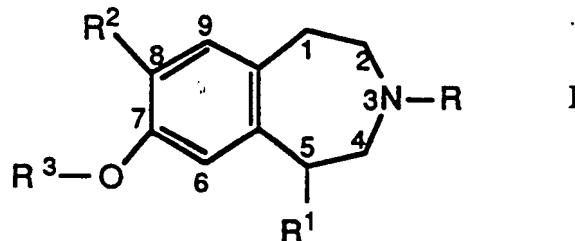
While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

25

WE CLAIM:

1. A compound having the structural formula I

5



and the pharmaceutically acceptable salts thereof,

wherein:

R represents H, (C₁-C₄)alkyl, allyl or cyclopropylmethyl;

10 R¹ represents C₃-, C₄-, C₅-, C₇- or C₈- cycloalkyl or (C₅-C₈) cycloalkenyl;

R² represents (C₁-C₄) alkyl;

R³ represents R², H, R² CO or ArNHCO;

15 Ar represents unsubstituted phenyl or phenyl substituted by one or more of halogen, R², CF₃, NH₂, NHR², NR²R² or NO₂ or combinations thereof.

2. A compound according to claim 1, wherein R¹ is (C₅-C₈) cycloalkenyl and R² is CH₃.

20

3. A compound according to claim 1 wherein R is CH₃, R¹ is cyclohexenyl, R² is CH₃ and R³ is H or CH₃.

25

4. A compound according to claim 1, said compound being selected from:

(±)-5-cyclopent-3'-en-1'-yl-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7-ol,

30 (±)-5-(cyclohex-1'-en-1'-yl)-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
(±)-5-(cyclohepta-2',4',6'-trien-1'-yl)-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

(±)-5-(cyclohex-2'-en-1'-yl)-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,

(\pm)-5-cyclopentyl-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol,
(\pm)-5-(cyclopent-2'-en-1'-yl)-3,8-dimethyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-ol, and the stereoisomers thereof;
and the pharmaceutically acceptable salts of the foregoing.

5. A pharmaceutical composition comprising as active ingredient an effective amount of a compound of any of the claims
10 1-4 together with a pharmaceutically acceptable carrier useful for treating psychoses or depression or for effecting analgesia or for use as an anti-psychotic and a pharmaceutically acceptable carrier therefor.

6. The use of a compound as claimed in any
15 one of claims 1 to 4 for the preparation of a pharmaceutical composition for use in treatment of psychoses or depression, or for effecting analgesia, in particular for use as an antipsychotic.

7. A method of treatment selected from one to
20 the following methods (a) to (c):

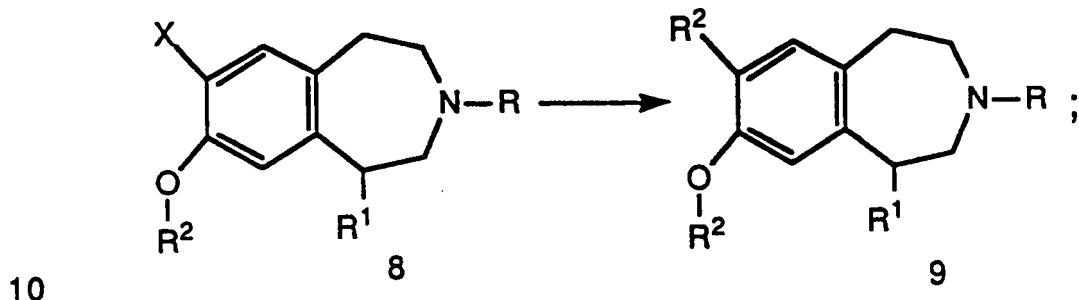
25 (a) treating psychoses in a mammal by administering to the mammal an antipsychotic effective amount of a compound as claimed in claim 1 or a pharmaceutical composition thereof,

30 (b) treating depression in a mammal by administering to the mammal an antidepressive effective amount of a compound as claimed in claim 1 or a pharmaceutical composition thereof, and

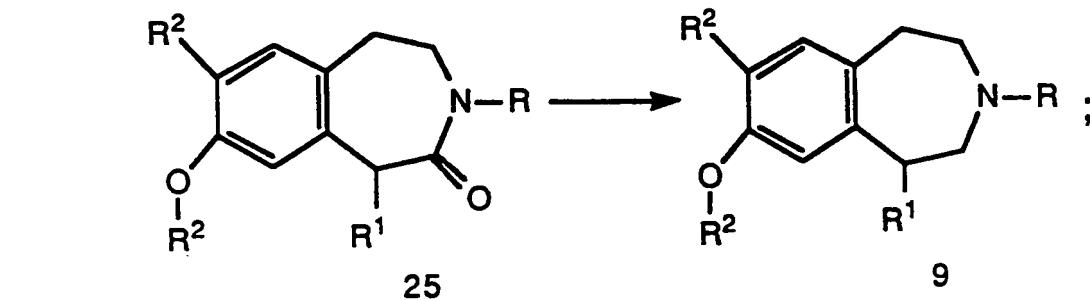
35 (c) providing for analgesia in a mammal by administering to the mammal an analgesically effective amount of a compound as claimed in claim 1 or a pharmaceutical thereof.

8. A process for the preparation of a compound represented by formula I of claim 1, which process comprises a process selected from the following processes A to C:

5 A: Alkylation of a compound of formula 8 to form a compound of formula 9:

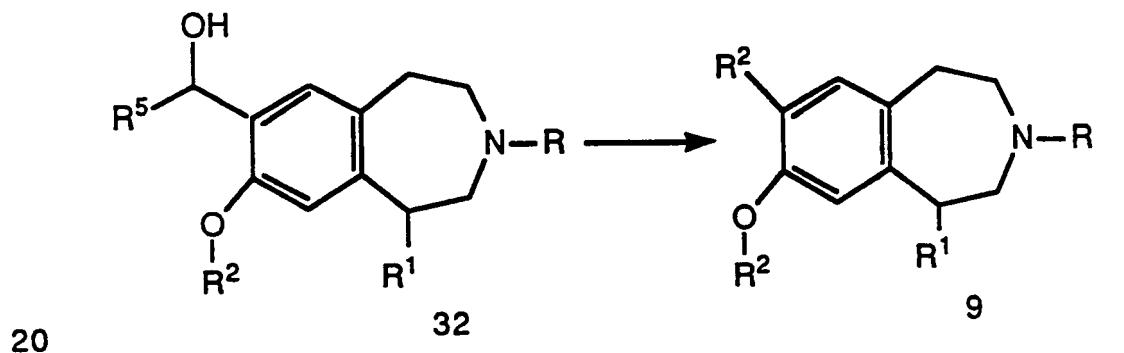


B: Reduction of a compound of formula 25 to form a compound of formula 9



and

C: Reduction of a compound of formula 32 to form a compound of formula 9



wherein R¹ m R², R³ and R are as defined in claim 1, R⁵ is (C₁-C₃) alkyl or H and said process is followed as desired by conversion of
5 compound 9 into compound of formula 1 set forth in claim 1.

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)⁶

According to International Patent Classification (IPC) or to both National Classification and IPC
 Int.C1.5 C 07 D 223/16 A 61 K 31/55

II. FIELDS SEARCHEDMinimum Documentation Searched⁷

Classification System	Classification Symbols
Int.C1.5	C 07 D 223/00

Documentation Searched other than Minimum Documentation
 to the Extent that such Documents are Included in the Fields Searched⁸

III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹

Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
X, Y	EP,A,0285919 (SCHERING CORPORATION) 12 October 1988, see the whole document (cited in the application) ---	1-6,8
Y	European Journal of Pharmacology, vol. 128, nr. 3, 09 September 1986, (Amsterdam, NL), A. Barnett et al.: "Relative Activities of SCH 23390 and its Three Tests for D1/DA1, Dopamine Receptor Antagonism", pages 249-253, see the whole article -----	1-6,8

¹⁰ Special categories of cited documents :¹⁰

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

02-10-1991

Date of Mailing of this International Search Report

22 OCT 1991

International Searching Authority

EUROPEAN PATENT OFFICE

Signature of Authorized Officer

Mme N. KUIPER

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claim numbers 7 because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. Claim numbers the second and third sentences of PCT Rule 6.4(a). because they are dependent claims and are not drafted in accordance with

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING²

This International Searching Authority found multiple inventions in this International application as follows:

1. As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application
2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:
3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- The additional search fees were accompanied by applicant's protest.
 No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9104046
SA 49406**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/10/91. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0285919	12-10-88	AU-A-	1596488	02-11-88
		EP-A-	0357641	14-03-90
		JP-T-	2502723	30-08-90
		WO-A-	8807526	06-10-88
		US-A-	5015639	14-05-91